A. pH - Partition Theory (Cont.):

3- A microclimate pH, that exists on the surface of intestinal mucosa and is lower than that of the luminal pH of the small intestine.

B. Lipid solubility of drugs:

- Some drugs are poorly absorbed after oral administration even though they are non-ionized in small intestine. Low lipid solubility of them may be the reason.
- The best parameter to correlate between water and lipid solubility is **partition coefficient**.

Partition coefficient (p) = [L] conc / [W] conc

where, [L] conc is the concentration of the drug in lipid phase.

[W] conc is the concentration of the drug in aqueous phase.

- The higher p value, the more absorption is observed.

C. Drug Dissolution:

- Many drugs are given in solid dosage forms and therefore must dissolve before absorption can take place.



- If dissolution is the slow, it will be the rate determining step (the step controlling the overall rate of absorption) then factors affecting dissolution will control the overall process.

C. Drug Dissolution (cont.):

- Drug dissolution is considered to be diffusion controlled process through a stagnant layer surrounding each solid particle.

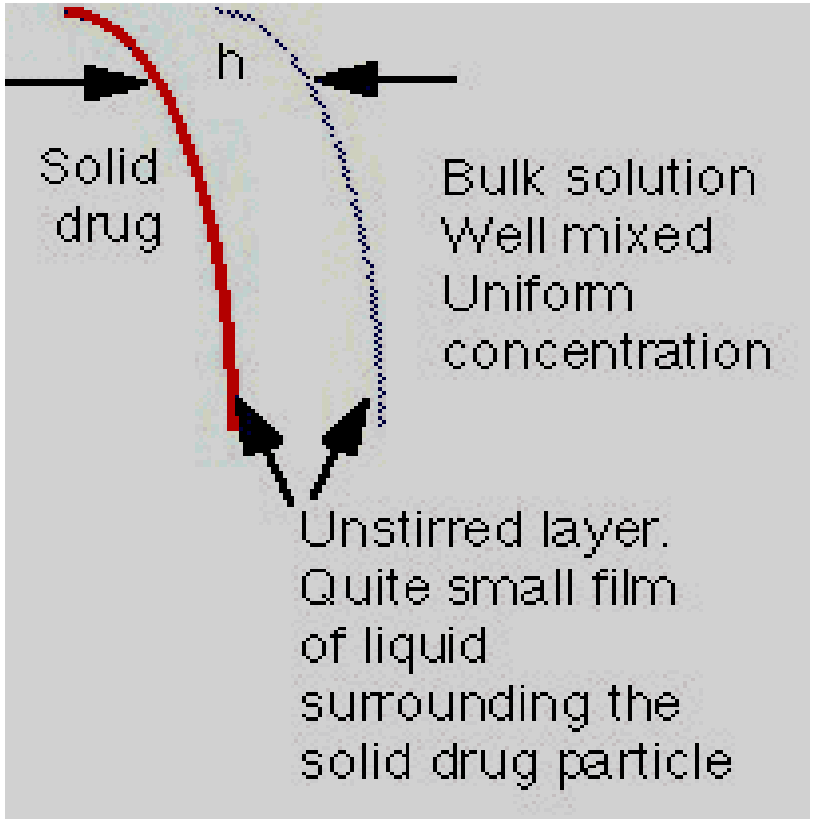


Diagram Representing Diffusion Through the Stagnant Layer

C. Drug Dissolution (cont.):

- The dissolution of drugs can be described by the **Noyes-Whitney equation:**

$$\text{Rate of Solution} = \frac{D \bullet A \bullet (Cs - Cb)}{h}$$

- Where D is the diffusion coefficient, A the surface area, Cs the solubility of the drug, Cb the concentration of drug in the bulk solution, and h the thickness of the stagnant layer.
-If Cb is much smaller than Cs then we have so-called "Sink Conditions" and the equation reduces to

$$\text{Rate of Solution} = \frac{D \bullet A \bullet Cs}{h}$$

C. Drug Dissolution (cont.):

Factors affecting drug dissolution in the GIT:

I Physiological factors affecting the dissolution rate of drugs:

- The environment of the GIT can affect the parameters of the Noyes-Whitney equation and hence the dissolution rate of a drug.

A- Diffusion coefficient, D:

- Presence of food in the GIT → increase the viscosity of the gastrointestinal fluids → reducing the rate of diffusion of the drug molecules away from the diffusion layer surrounding each undissolved drug particles **(↓ D)**

→ decrease in dissolution rate of a drug.

C. Drug Dissolution (cont.):

B- Drug surface area, A:

Surfactants in gastric juice and bile salts increase the wettability of the drug drug → increase the solubility via micellization.

C. The thickness of diffusion layer, h:

An increase in gastric and/or intestinal motility decrease the thickness of diffusion layer around each drug particle → increase the dissolution rate of a drug.

D.The concentration, C, of drug in solution in the bulk of the gastrointestinal fluids:

C. Drug Dissolution (cont.):

Increasing the rate of removal of dissolved drug by absorption through the gastrointestinal-blood barrier and increasing the intake of fluid in the diet → will decrease in C → rapid dissolution of the drug.

II Physicochemical factors affecting the dissolution rate of drugs:

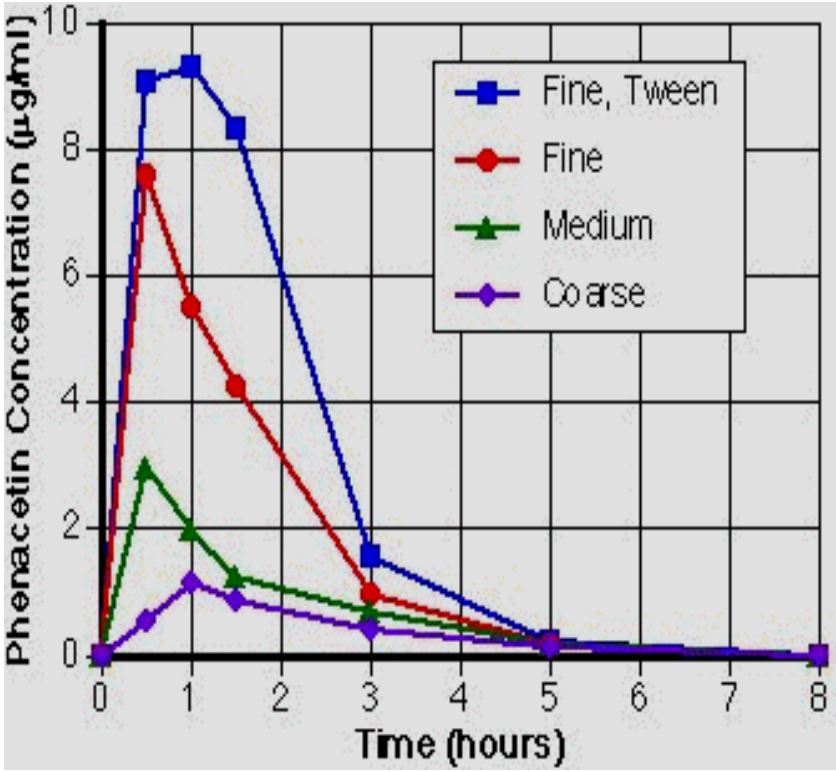
A- Surface area, A:

- The smaller the particle size → the greater the effective surface area of drug particle → the higher the dissolution rate.

C. Drug Dissolution (cont.):

- *Methods of particle size reduction include:* mortar and pestle, mechanical grinders, mills, solid dispersions in readily soluble materials (PEG's).

-However very small particles can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption.



C. Drug Dissolution (cont.):

B-Diffusion coefficient, D:

The value of D depends on the size of the molecule and the viscosity of the dissolution medium.

C- Solubility in the diffusion layer, C_s:

- The dissolution rate of a drug is directly proportional to its intrinsic solubility in the diffusion layer surrounding each dissolving drug particle.

C. Drug Dissolution (cont.):

D- Salts:

- **Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.**
- The dissolution rate of a weakly acidic drug in gastric fluid (pH 1 – 3.5) will be relatively low.
- If the pH in the diffusion layer increased, the solubility, $C_{s,}$ of the acidic drug in this layer, and hence its dissolution rate in gastric fluids would be increased.

C. Drug Dissolution (cont.):

- The pH of the diffusion layer would be increased if the chemical nature of the weakly acidic drug was changed from that of the free acid to a basic salt (the sodium or potassium form of the free acid.

- The pH of the diffusion layer would be higher (5-6) than the low bulk pH (1-3.5) of the gastric fluids because of the neutralizing action of the strong (Na^+, K^+) ions present in the diffusion layer.

- The drug particles will dissolve at a faster rate and diffuse out of the diffusion layer into the bulk of the gastric fluid, where a lower bulk pH.

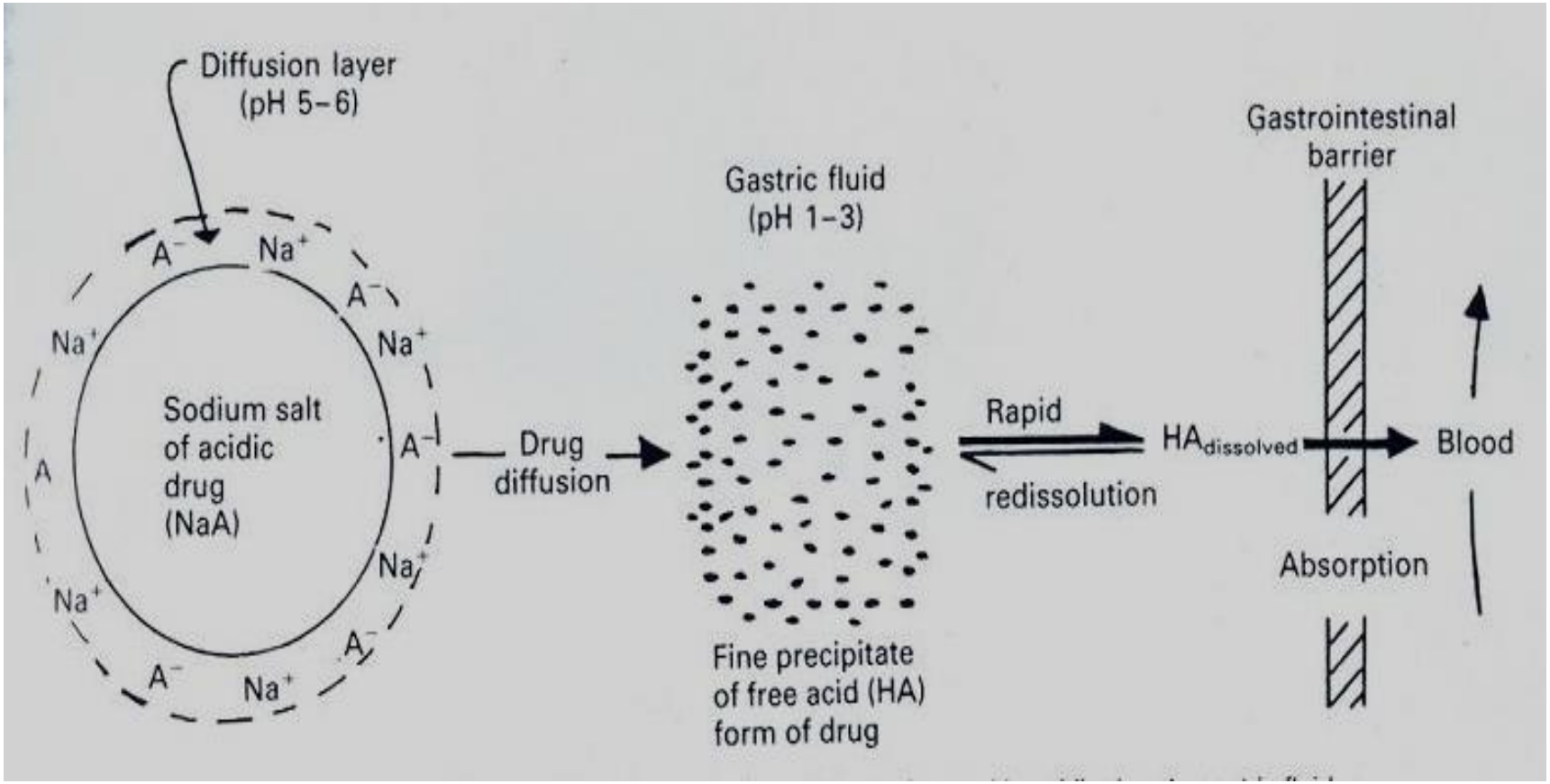
C. Drug Dissolution (cont.):

- Thus the free acid form of the drug in solution, will precipitate out , leaving a saturated solution of free acid in gastric fluid.

This precipitated free acid will be in the form of:

- very fine,
- non-ionized,
- wetted particles which have a very large surface area in contact with gastric fluids, facilitating rapid redissolution when additional gastric fluid is available.

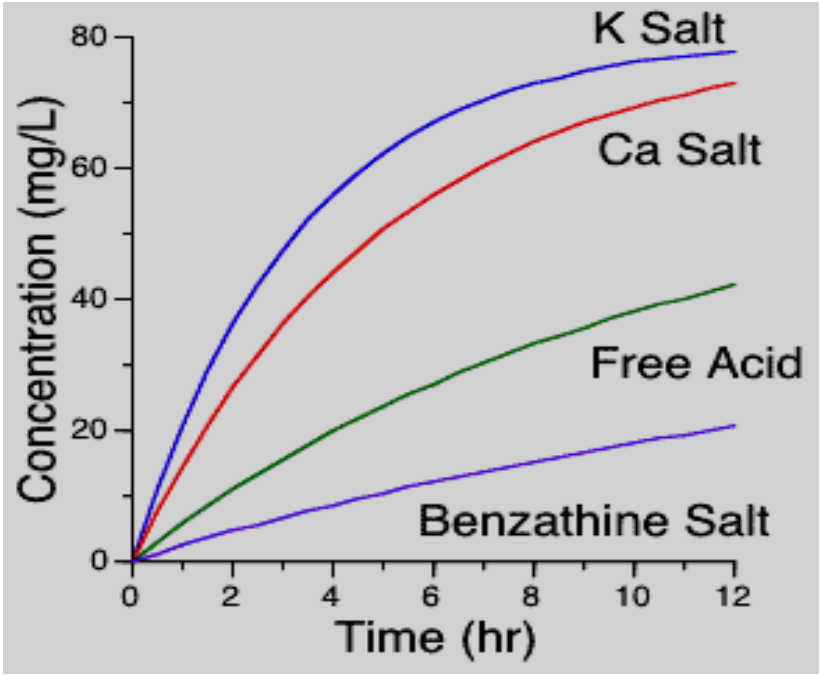
Drug Dissolution (cont.):

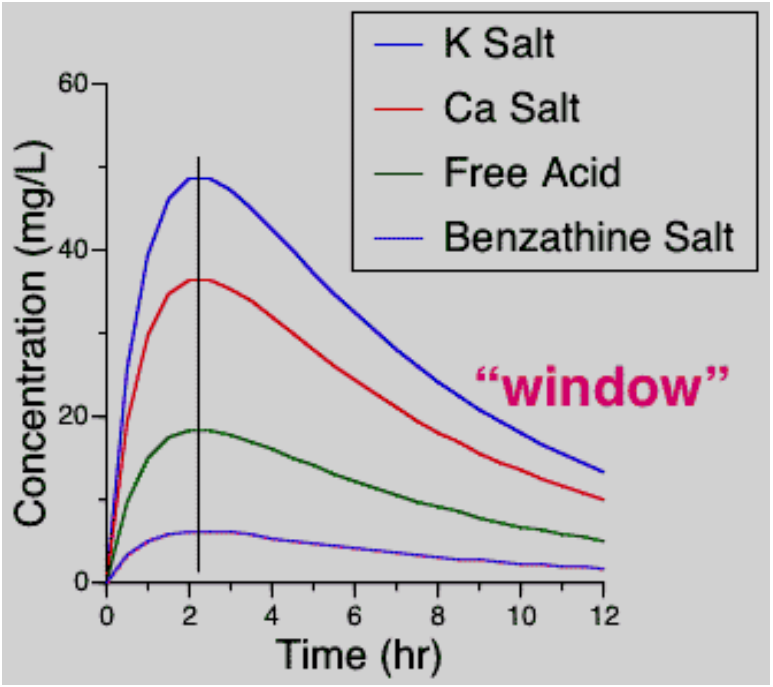


Dissolution process of a salt form of a weakly acidic drug in gastric fluid.

Drug Dissolution (cont.):

- One example is the dissolution and bioavailability profiles of Penicillin V with various salts.





These results might support the use of the benzathine or procaine salts for IM depot use and the potassium salt for better absorption orally.

Drug Dissolution (cont.):

E- Crystal form:

1- Polymorphism:

- Some drugs exist in a number of crystal forms or polymorphs. These different forms may have different solubility properties and thus different dissolution characteristics.
- Chloramphenicol palmitate is one example which exists in three crystalline forms A, B and C.

A → is the stable polymorph

B → is the metastable polymorph (more soluble)

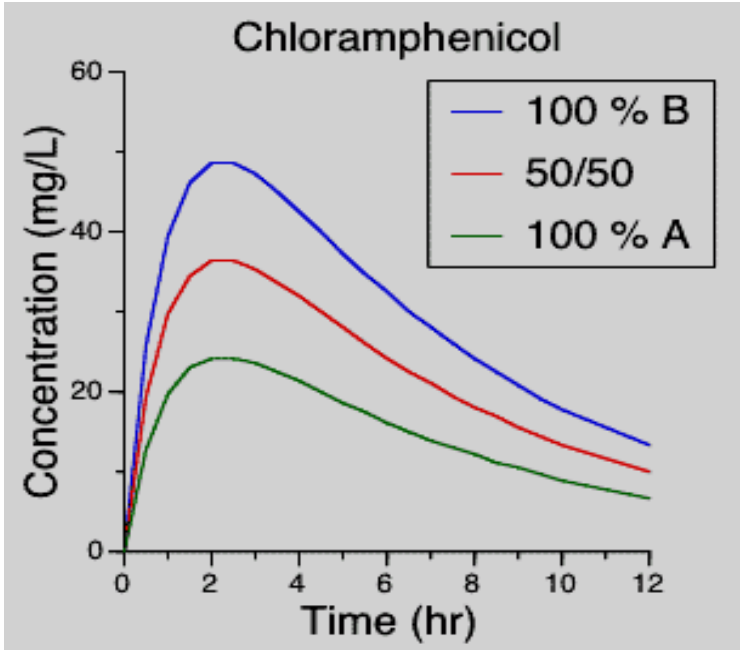
C → is the unstable polymorph

- The plasma profiles of chloramphenicol from oral suspensions containing different proportions of

Drug Dissolution (cont.):

Polymorphic forms A and B were investigated.

-The extent of absorption of Chloramphnicol increases as the Proportion of the polymorphic form B is increased in each suspension. This is attributed to the more rapid Dissolution of the metastable Polymorphic form B.



- Shelf-life could be a problem as the more soluble (less stable) form may transform into the less soluble form (more stable).

Drug Dissolution (cont.):

2- Amorphous solid:

- The amorphous form dissolves more rapidly than the corresponding crystalline form.
- The more soluble and rapidly dissolving amorphous form of novobiocin antibiotic was readily absorbed following oral administration of an aqueous suspension to humans. However, the less soluble and slower-dissolving crystalline form of novobiocin was not absorbed (therapeutically ineffective).
- The amorphous form of novobiocin slowly converts to the more stable crystalline form, with loss of therapeutic effectiveness.

Drug Dissolution (cont.):

3- Solvates:



Solvates: If the drug is able to associate with solvent molecules to produce crystalline forms known as solvates.

Hydrates: drug associates with water molecules.

- The greater the solvation of the crystal, the lower are the solubility and dissolution rate in a solvent identical to the solvation molecules.

Drug Dissolution (cont.):

- The faster-dissolving anhydrous form of ampicillin was absorbed to a greater extent from both hard gelatin capsules and an aqueous suspension than was the slower-dissolving trihydrate form.

D- Drug stability and hydrolysis in GIT:

- Drugs that are susceptible to acidic or enzymatic hydrolysis in the GIT, suffer from reduced bioavailability.
- How to protect drugs (erythromycin) from degradation in gastric fluid ??

1 Preparing enteric coated tablets containing the free base of erythromycin. The enteric coating resists gastric fluid but disrupts or dissolves at the less acid pH range of the small intestine.





2 The administration of chemical derivatives of the parent drug. These prodrugs (erythromycin stearate) exhibit limited solubility in gastric fluid, but liberate the drug in the small intestine to be absorbed.

E- Complexation:

- Complexation of a drug may occur within the dosage form and/or in the gastrointestinal fluids, and can be benefecial or deterimental to absorption.

1 Intestinal mucosa (mucin) + Streptomycin = poorly absorbed complex

2 Calcium + Tetracycline = poorly absorbed complex (Food-drug interaction)

3- Carboxyl methylcellulose (CMC) + Amphetamine = poorly absorbed complex (tablet additive – drug interaction)

4- Lipid soluble drug + water soluble complexing agent = well-absorbed water soluble complex (cyclodextrin)

F- Adsorption:

- Certain insoluble susbstances may adsorbed co-administrated drugs leading to poor absorption.
- Charcoal (antidote in drug intoxication).
- Kaolin (antidiarrhoeal mixtures)
- Talc (in tablets as glidant)



III Formulation Factors Affecting Oral Absorption:

- The role of the drug formulation in the delivery of drug to the site of action should not be ignored.
- Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

A. *Solution dosage forms:*

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

III Formulation Factors Affecting Oral Absorption (Cont.):

- Some drugs which are poorly soluble in water may be:

1. dissolved in mixed water/alcohol or glycerol solvents (cosolvency),

2. given in the form of a salt (in case of acidic drugs)

3. An oily emulsion or soft gelatin capsules have been used for some compounds with lower aqueous solubility to produce improved bioavailability.

III Formulation Factors Affecting Oral Absorption (Cont.):

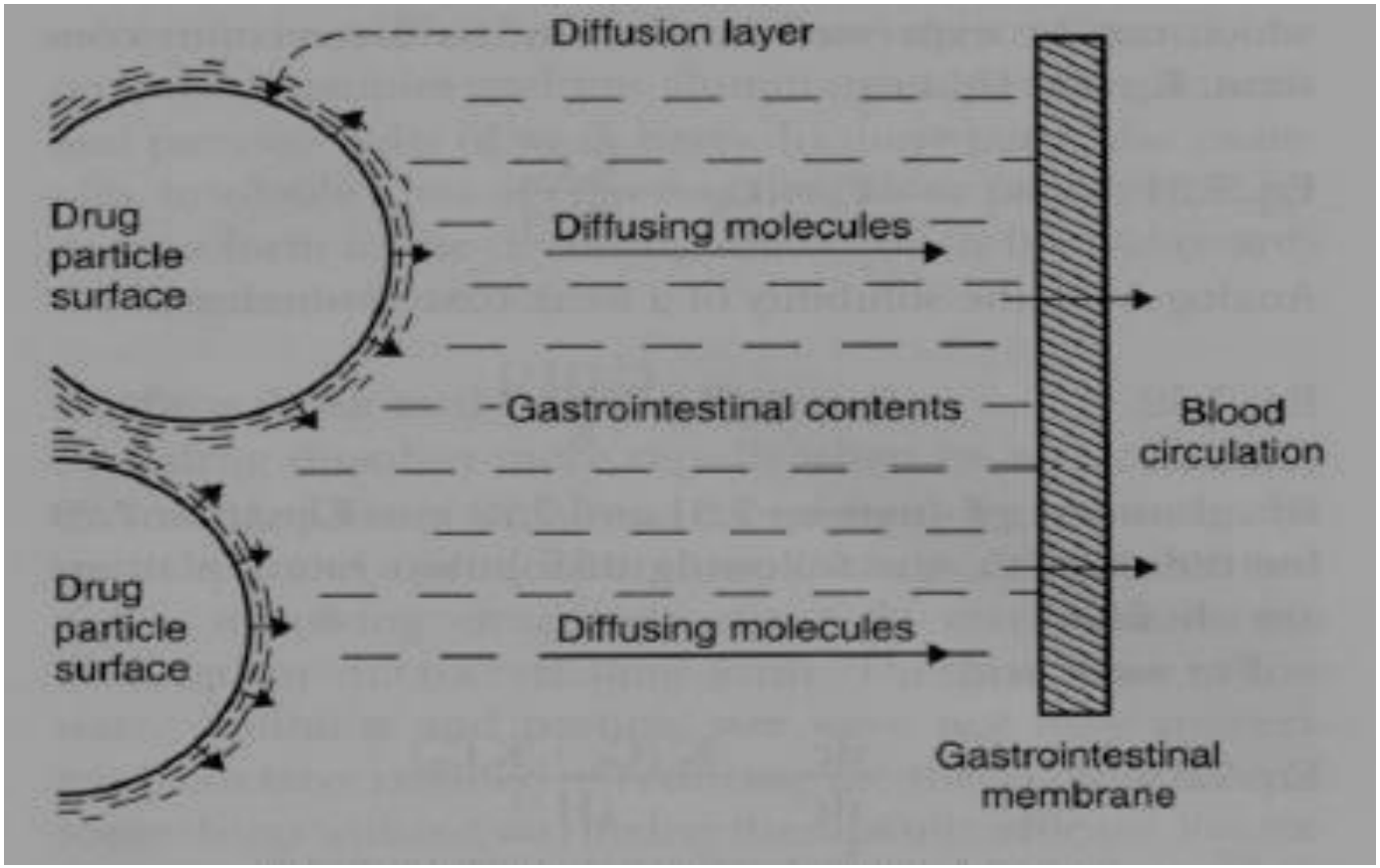
B. Suspension dosage forms:

- A well formulated suspension is second to a solution in terms of superior bioavailability.

- A suspension of a finely divided powder will maximize the potential for rapid dissolution.
- A good correlation can be seen for particle size and absorption rate.

- The addition of a surface active agent will improve the absorption of very fine particle size suspensions.

III Formulation Factors Affecting Oral Absorption (Cont.):



Absorption of drugs from aqueous suspensions

III Formulation Factors Affecting Oral Absorption (Cont.):



C. Capsule dosage forms:

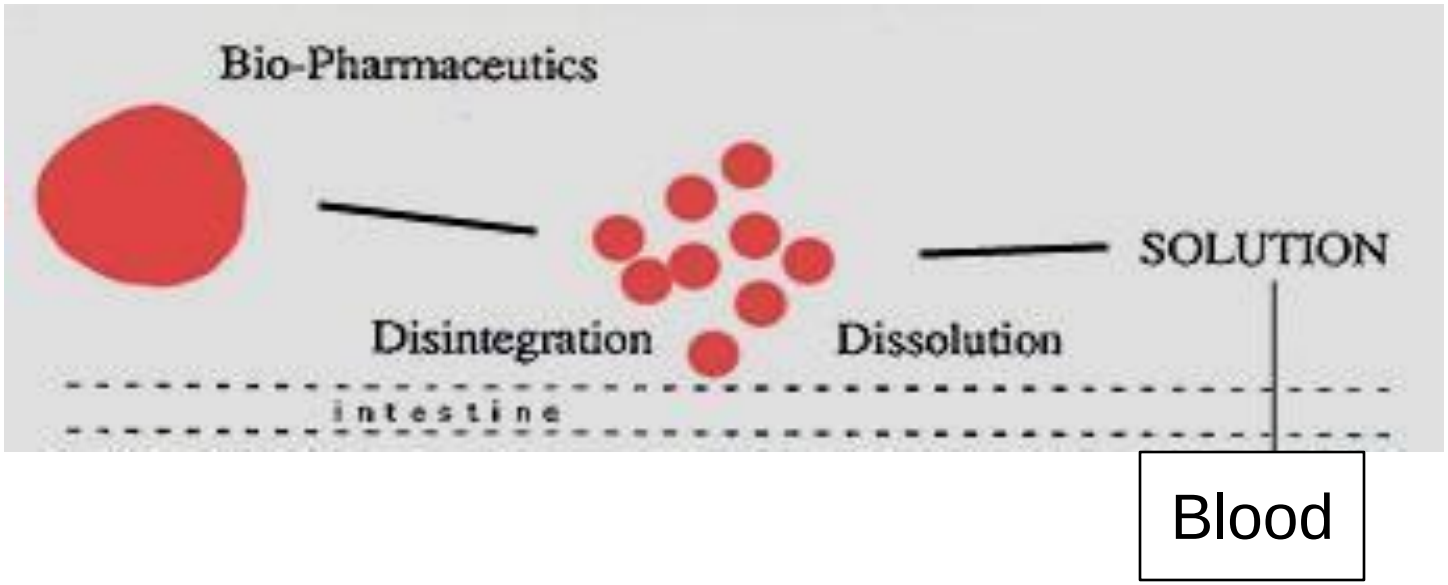
- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.

- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.

- Tightly packed capsules may have reduced dissolution and bioavailability.

III Formulation Factors Affecting Oral Absorption (Cont.):

D. Tablet dosage forms:



III Formulation Factors Affecting Oral Absorption (Cont.):

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.



1-Ingredients

Drug : may be poorly soluble, hydrophobic

Lubricant : usually quite hydrophobic

Granulating agent : tends to stick the ingredients together

Filler: may interact with the drug, etc., should be water soluble

Wetting agent : helps the penetration of water into the tablet

Disintegration agent: helps to break the tablet apart